# Iron-Catalyzed Anti-Markovnikov Hydroamination and Hydroamidation of Allylic Alcohols

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**ABSTRACT:** Hydroamination allows for the direct access to synthetically important amines. Controlling the selectivity of the reaction with efficient, widely applicable and economic catalysts remains challenging, however. This paper reports an iron-catalyzed formal anti-Markovnikov hydroamination and hydroamidation of allylic alcohols, which yields γ-amino and γ-amido alcohols, respectively. Homoallylic alcohol is also feasible. The catalytic system, consisting of a pincer Fe-PNP complex (1-4 mol%), a weak base and a nonpolar solvent, features exclusive anti-Markovnikov selectivity, broad substrate scope (>70 examples), and good functional group tolerance. The reaction could be performed at gram scale and applied to the synthesis of drug molecules and heterocyclic compounds. When chiral substrates are used, the stereochemistry and enantiomeric excess are retained. Further application of the chemistry is seen in the functionalization of amino acids, natural products as well as existing drugs. Mechanistic studies suggest that the reaction proceeds via two cooperating catalytic cycles, with the iron complex catalyzing a dehydrogenation/hydrogenation process while the amine substrate acting as an organocatalyst for the Michael addition step.

## INTRODUCTION

Hydroamination of alkenes is a direct, atom-economic approach to accessing amines, the most ubiquitous functionalities found in fine chemicals, pharmaceuticals and agrochemicals (Figure 1a).[1] As such, it has been extensively studied over the last two decades or so, expanding into a wide variety of amines and alkenes.[2] Rather surprisingly, however, examples of hydroamination of allylic alcohols are rare. Allylic alcohol is a readily available commodity chemical.[3] Bearing a hydroxy and olefinic functionality, allyl alcohol and the derivatives have been used as an intermediate in various chemical synthesis. Hydroamination of the C=C double bonds of allylic alcohols would generate highly valuable β-[4] or γ-[5] amino alcohols, depending on the reaction being Markovnikov or anti-Markovnikov selective. *To the best of our knowledge, however, there appears to be no example of Markovnikov hydroamination of allylic alcohols in the literature, and only one report on anti-Markovnikov hydroamination is known*, which, catalyzed by a Ru complex, proceeds via a hydrogen-borrowing process, according to Oe and co-workers[6] (Figure 1b). Herein, we disclose the first examples of iron-catalyzed hydroamination of allylic alcohols with exclusive anti-Markovnikov selectivity to produce γ-amino alcohols. The hitherto unprecedented hydroamidation of allylic alcohols is also demonstrated (Figure 1c).

Hydroamination of terminal alkenes normally affords products with Markovnikov selectivity.[2] Whilst significant

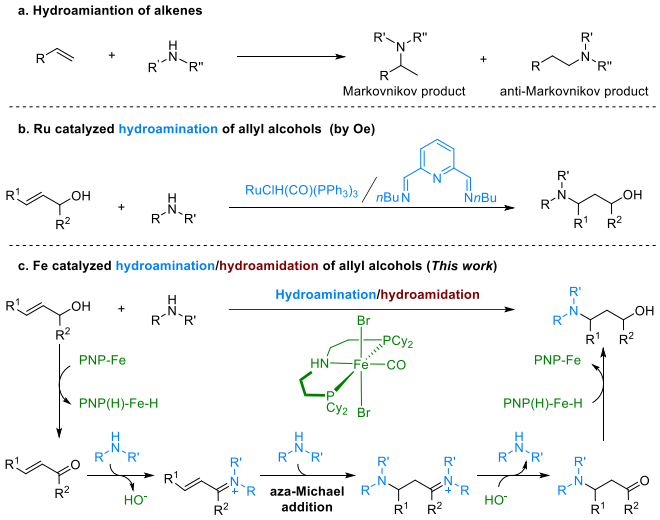



Figure 1. Hydroamination of alkenes and Fe-catalyzed formal anti-Markovnikov hydroamination/hydroamidation of allyl alcohols.

advances have been made in anti-Markovnikov hydroamination in the last a few years, controlling the selectivity remains challenging, due to the intrinsic electronic and steric bias embedded in the reacting alkene and amine substrates.[7] Notable strategies in directing the amination in the anti-Markovnikov fashion include substrate and catalyst control,[8] use of electrophilic amines in conjunction with a hydride source,[2w,9] and photocatalysis and related means to generate amine radicals.[10] In addition, some indirect, formal anti-

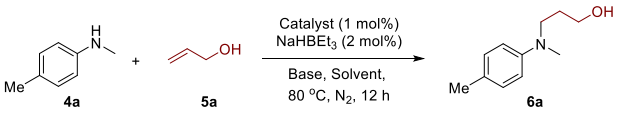
Markovnikov hydroamination strategies have been put forward, such as hydroboration/amination,[11] hydrozirconation/amination,[12] and Wacker oxidation/reductive amination.[13] Despite the advances made, new catalysts are still highly desirable, which should not only deliver exclusive anti-Markovnikov selectivity, but also exhibit a wider substrate scope and functional-group tolerance in hydroamination, with the additional advantage of being less expensive and less toxic.

During our studies on dehydrogenative reactions,[14] we found that a Fe-PNP pincer complex could catalyze the reversible dehydrogenation of alcohols and hydrogenation of aldehydes.[14f] The hydrogenation and dehydrogenation abilities of iron complexes,[15] including particularly iron pincer complexes,[16] have also been found by other groups. However, the use of Fe-PNP complexes to activate alcohols for coupling reactions are rare.[14f,17] We envisioned that the ability of the Fe-PNP complex might be harnessed to temporarily activate alcohols for coupling[18] with amines. In particular, an allylic alcohol could be dehydrogenated by the Fe-PNP complex to give an α,β-unsaturated carbonyl compound and an iron hydride species, and in the presence of an amine, Michael addition to the carbonyl followed by reduction of the resulting amino-carbonyl adduct with the iron hydride would formally lead to an anti-Markovnikov product, an γ-amino alcohol (Figure 1c).[18] We note that once produced, the α,β-unsaturated carbonyl compound could also in situ condense with a secondary amine to form an iminium cation, activating the carbonyl compound toward nucleophilic addition, as is often invoked in organocatalysis (Figure 1c).[19]

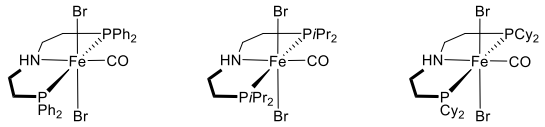
To implement this hydrogen-borrowing strategy[17c,20] for anti-Markovnikov hydroamidation of allylic alcohols, the catalyst ought to be chemoselective, avoiding catalyzing allylic isomerization, allylic substitution,[21] and reduction of C=C or C=N bonds, in addition to being resilient to possible poisoning by the amine substrate and product (Figure 1c). Whilst the strategy has been successfully demonstrated by Oe and co-workers with a Ru catalyst in hydroamination, primarily with secondary amines (only one example of a primary amine, with considerably reduced product yield),[6] it has not been tested with any earth-abundant base metal catalysts. For a reaction as important as hydroamination with enormous potential to be used in various chemical synthesis, an iron-based catalyst would be particularly appealing due to the low cost and low toxicity of iron. *We show here that the Fe-PNP complex is an excellent catalyst for the formal anti-Markovnikov hydroamination as well as hydroamidation of allylic alcohols, displaying broad substrate scope, good functional group tolerance, and scalability (76 examples; gram scale).*[22] The protocol provides a practical alternative route to the synthesis of γ-amino and γ-amido alcohols, which are useful for making many bioactive molecules.[5]

## Results and discussion

**Table 1. Optimization of conditions for hydroamination**[a]




| Entry | Catalyst | Base | Solvent | Yield (%) |
|---|---|---|---|---|
| 1 | **1** | MeONa | toluene | 5 |
| 2 | **2** | MeONa | toluene | 23 |
| 3 | **3** | MeONa | toluene | 27 |
| 4 | **3** | EtONa | toluene | 7 |
| 5 | **3** | *t*-BuOK | toluene | 8 |
| 6 | **3** | NaOH | toluene | 30 |
| 7 | **3** | KOH | toluene | 27 |
| 8 | **3** | $K_2CO_3$ | toluene | 55 |
| 9 | **3** | $K_3PO_4$ | toluene | 66 |
| 10 | **3** | $K_3PO_4$ | MeCN | 6 |
| 11 | **3** | $K_3PO_4$ | dioxane | 24 |
| 12 | **3** | $K_3PO_4$ | DMF | 24 |
| 13 | **3** | $K_3PO_4$ | THF | 37 |
| 14 | **3** | $K_3PO_4$ | cyclohexane | 76 |
| 15[b] | **3** | $K_3PO_4$ | cyclohexane | 84 |
| 16[c] | **3** | $K_3PO_4$ | cyclohexane | **99** |




[a] Reaction conditions: Catalyst (1 mol%), $NaHBEt_3$ (2 mol%), *N*-methyl-*p*-toluidine (0.5 mmol), allyl alcohol (0.75 mmol), base (20 mol%), solvent (2 mL), 80 °C, 12 h. Yields were determined by $^1H$ NMR with 1,3,5-trimethoxybenzene as internal standard. [b] With 40 mol% $K_3PO_4$. [c] With 40 mol% $K_3PO_4$ and 1.5 mmol of allyl alcohol.

**Identification of an iron catalytic system.** Iron complexes bearing pincer PNP ligands are known to be efficient catalysts for hydrogenation and dehydrogenation reactions.[16] In particular, we and other groups have shown that the pincer complexes **1-3** are effective for borrowing-hydrogen reactions that involve alcohol dehydrogenation. We therefor set out to examine the hydroamination of the allyl alcohol **5a** with *N*-methyl-*p*-toluidine **4a** with these iron complexes as precatalyst, using MeONa as base and a catalytic amount of a boron hydride as an activating agent in toluene (Table 1). Previous studies have indicated the necessity of converting the bromo complexes into active iron hydrides before dehydrogenation takes place.[14f,16] The γ-amino alcohol **6a** was indeed observed, with the more electron-rich **2** and **3** affording a better yield (Table 1 entries 1-3). We also evaluated a range of other metal complexes, none of which were more active than **3** under the conditions employed (See Table S1 in SI for details). Our subsequent study was therefore focused on optimization of the conditions for **3**. Screening of various parameters revealed that the base and solvent play a

particularly important role in the hydroamination (Table 1, entries 4-15). Most notably, the reaction benefits from a weaker base and a non-coordinating solvent, with the combination of $K_3PO_4$ with cyclohexane affording the best yield of **6a**. Thus, the hydroamination of **5a** (1.5 mmol) with **4a** (0.5 mmol) furnished **6a** in 99% yield in the presence of **3** (1 mol%), $NaHBEt_3$ (2 mol%), and $K_3PO_4$ (40 mol%) in cyclohexane (2.0 mL) at 80 °C for 12 h (entry 16). It is noted that under the optimized conditions, **2** and **3** showed negligible difference in activity (Scheme S2, SI).

**Hydroamination with aryl amines**. With the optimized catalytic system in hand, we went on to examine the substrate scope of the reaction, firstly by reacting allyl alcohol with various aryl amines (Figure **2**). As can be seen, the hydroamination works, affording a range of γ-amino alcohols with good to excellent yields. The electronic properties of the amine substrates affect considerably the rate of the reaction. This is clearly seen in *N*-methylaryl amines, with those bearing electron donating substituents on the phenyl moiety affording higher product yields in a shorter reaction time than those having electron withdrawing substituents (**6a**, **6d** vs **6e**-**6h**). Similarly, the steric effect is also pronounced. Thus, a longer reaction time was required for the *N*-methylphenyl amine with a *meta*-methyl substituent (**6c**) and little reaction took place for the *ortho*-methyl substituted analogue. Replacing the methyl group of *N*-methylphenyl amines with bulkier groups also rendered the reaction slower (**6i**-**6k**). Pleasingly, good yields were observed for heterocyclic aryl amines, such as the 1,2,3,4-tetrahydroquinoline derivatives, indoline, and 1,2,3,4-tetrahydroquinoxaline (**6l**-**6o**). For the latter, the bis-alkylated product was obtained (**6o**).

*Primary aryl amines could also be used for the hydroamination*. However, a higher catalyst loading, temperature and longer reaction time were required to obtain acceptable yields (**6p**-**6s**). The different activity observed for the secondary and primary amines may stem from the former being able to activate the α,β-unsaturated aldehyde intermediate toward the aza-Michael addition (*vide infra*).

**Hydroamination with aliphatic amines.** Compared with aryl amines, aliphatic amines may be expected to be more difficult to react, due to their stronger coordination with and hence more prone to poisoning of metal complexes. Figure 3 shows, delightfully, that a range of diverse aliphatic amines can be readily employed for hydroamination of allyl alcohol under the catalysis of **3**. In general, secondary aliphatic amines showed good activity and clean reactions (**8a**-**8d**), although the low boiling point of some products affected their isolated yield (**8a**, **8b**). A pyridine heterocycle is tolerated (**8g**). Notably, chiral γ-amino alcohols were formed when chiral amines were used, with no erosion of the enantiomeric excess observed, although the isolated yields were only moderate possibly due to steric hindrance of the amine substrates (**8e**, **8f**).

Different from primary aryl amines, primary aliphatic

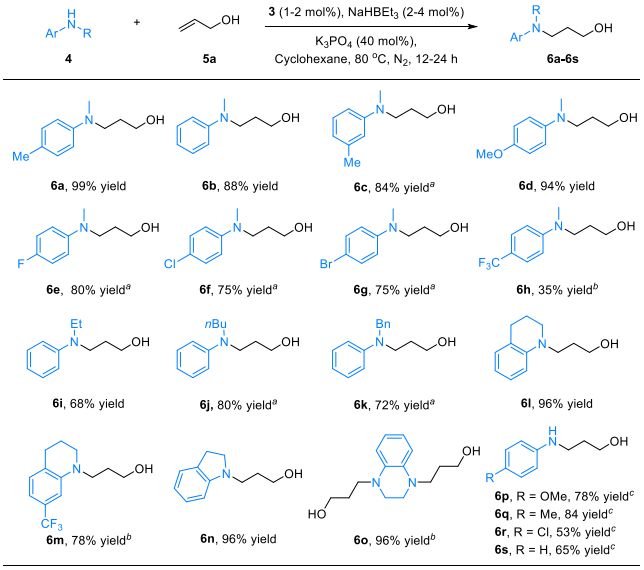



Figure 2. Hydroamination of allyl alcohol with arylamines. Reaction conditions: **3** (1 mol%), NaHBEt3 (2 mol%), amine (0.5 mmol), allylic alcohol (1.5 mmol), $K_3PO_4$ (40 mol%), cyclohexane (2 mL), 80 °C, 12 h, isolated yield. [a] The reaction time was 24 h. [b] With 2 mol% **3**, 4 mol% $NaHBEt_3$, 2.0 mmol allyl alcohol, 24 h. [c] With 5 mol% **3**, 10 mol% $NaHBEt_3$, 2.0 mmol allyl alcohol, 120 °C, 24 h.

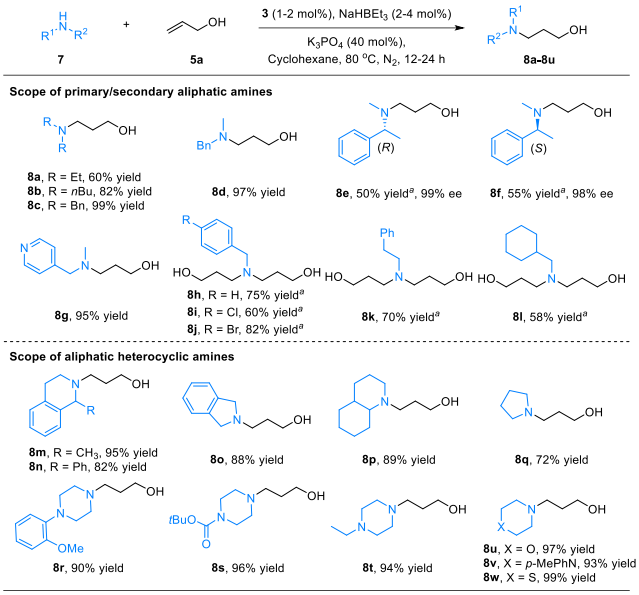



Figure 3. Hydroamination of allyl alcohol with aliphatic amines. Reaction conditions: **3** (1 mol%), $NaHBEt_3$ (2 mol%), amine (0.5 mmol), allylic alcohol (1.5 mmol), $K_3PO_4$ (40 mol%), cyclohexane (2 mL), 80 °C, 12 h, isolated yield. [a] With 2 mol% **3**, 4 mol% $NaHBEt_3$, 2.0 mmol allyl alcohol, 24 h.

amines led to *bis-alkylated products*, reflecting their enhanced nucleophilicity and decreased steric hindrance (**8h**-**8l**). These results are also different from those obtained with Oe's system, which afforded mono-alkylated product in low yield in one example.[6] Of further notice is that good to excellent yields were obtained for heterocyclic secondary aliphatic amines (**8m**-**8w**). Some of these products, which have not been reported via other hydroamination methods, may serve as valuable

intermediates for the synthesis of drug molecules (*vide infra*).

**Hydroamidation of allyl alcohol.** The hydroamidation of alkenes is generally more difficult than hydroamination, possibly due to the low nucleophilicity of amides. Indeed, examples of anti-Markovnikov hydroamidation are rare,[8x,10c,10f,10j,23] and in the case of allylic alcohols, neither Markovnikov nor anti-Markovnikov hydroamidation has been reported so far.[2t,2y,2z,2ab] As shown in Figure 4, under the catalysis of **3**, a range of amides underwent addition to allylic alcohol, furnishing γ-hydroxy amides in good yields, which can be used for the synthesis of heterocycles.[24] In comparison with the hydroamination above, harsher reaction conditions were required for the hydroamidation, however. Thus, a stronger base (MeONa), higher temperature (120 °C), and higher catalyst loading were employed for the primary amides (**10a-10g**). As with the hydroamination, the electron rich aryl amide (**10e**) afforded a better yield. Aliphatic primary amides are also viable, as exemplified by the reaction of **9g** affording **10g**.

A problem was encountered with secondary amides, the product of which underwent alcoholysis. For example, the hydroamidation with **9h** led to not only **10h** but also a side product **6s**. Consequently, lower yields were obtained for these substrates, even with careful control of reaction conditions (**10h-10l**). This shortcoming offers an opportunity for accessing γ-amino alcohols from the amides, however. Thus, hydroamidation of allyl alcohol with *N*-phenylacetamide followed by hydrolysis with a NaOH solution afforded **6s** in 74% yield (See section 3.9 in the SI for details).

**The scope of allylic alcohols.** Using morpholine as the amine partner, we further investigated the substrate scope of allylic alcohols. As can be seen from Figure 5, regardless of the pattern of substitution on the allylic

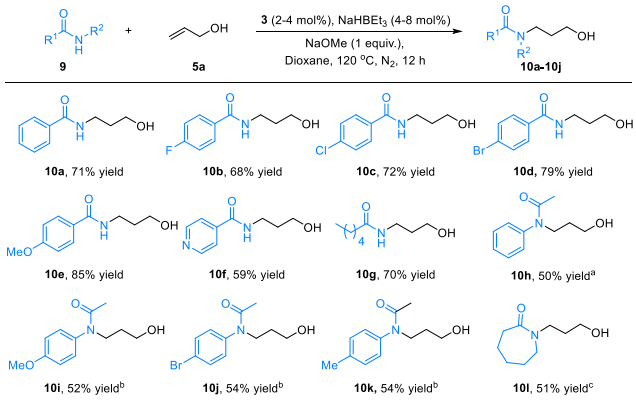



Figure 4. Hydroamidation of allyl alcohol with amides. Reaction conditions for **10a-10g**: **3** (2 mol%), $NaHBEt_3$ (4 mol%), amide (0.5 mmol), allyl alcohol (2.0 mmol), NaOMe (0.5 mmol), dioxane (2 mL), 120 °C, 12 h. [a] With 1.0 mmol allyl alcohol, CsOH·$H_2O$ (20 mol%), 4 Å MS (7 mg), toluene (2 mL), 70 °C, 24 h. [b] With **3** (4 mol%), $NaHBEt_3$ (8 mol%), 1.0 mmol allyl alcohol, CsOH·$H_2O$ (20 mol%), 4 Å MS (7 mg), toluene (2 mL), 70 °C, 48 h. [c] With **3** (4 mol%), $NaHBEt_3$ (8 mol%), toluene (2 mL), 130 °C, 48 h.

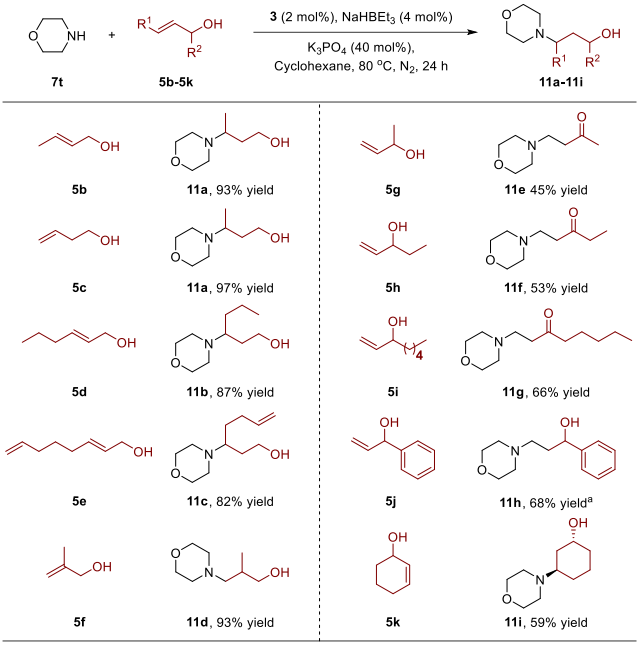



Figure 5. Hydroamination of different allylic alcohols and homoallylic alcohol with morpholine. Reaction conditions: **3** (2 mol%), $NaHBEt_3$ (4 mol%), morpholine (0.5 mmol), allylic alcohol (1.5 mmol), $K_3PO_4$ (40 mol%), cyclohexane (2 mL), 80 °C, 24 h. [a] With 2.0 mmol allylic alcohol, 60 °C, 48 h.

alcohol, the amine added to the γ-position of the allylic alcohols with good to excellent yields in all cases (**11a-11i**). Remarkably, a remote C=C double bond was tolerated and remained intact during the reaction (**11c**), and the homoallylic alcohol **5c** could be brought into the hydroamination, affording, in high yield, the same product **11a** as that from allylic alcohol **5b**. The reaction of **5c** suggests that *the Fe-catalytic system is capable of isomerization a C=C double bond.*[25] Furthermore, for α-alkyl substituted allylic alcohols, amino ketones instead of amino alcohols were formed as the products, albeit with lower yields (**11e-11g**). The reaction of the α-phenyl substituted allylic alcohol **5j** to give **11h** was carried out at a lower temperature of 60 °C, due to its instability under the reaction conditions. 2-Cyclohexenol is also a viable substrate, affording the cyclic amino alcohol **11i** in a moderate yield with exclusive *trans* selectivity (See SI for details).

**Functionalization of amino esters, natural products and drug molecules.** The versatility of the iron catalytic system was further demonstrated by functionalization of more complex molecules. Thus, as shown in Figure 6, various amino esters could be employed for the hydroamination of allylic alcohol, affording γ-hydroxy functionalized amino esters in moderate yields (**12a-12h**). Notably, the enantiomeric excess of the starting ester was retained, as demonstrated by **12h**.

Of further interest is that *natural products and drug molecules can be readily modified by the reaction in a late-stage fashion*. Thus, cytisine, a naturally occurring alkaloid, reacted with allyl alcohol under the iron catalysis to afford a hydroxyalkylated product **12i** in high yield. The drug molecules Troxipide used in treating gastroesopha-

geal reflux symptoms, and Amoxapine, Fluoxetine, Rolipram and Duloxetine, all with antidepressant activity, could be hydroxyalkylated with allyl alcohol in good to excellent yields (**12j-12n**). Not only could the hydroxyalkyl unit be expected to alter the property of these bioactive molecules, it also allows these molecules to be easily derivatized, raising the possibility of new applications in biological and medicinal studies.

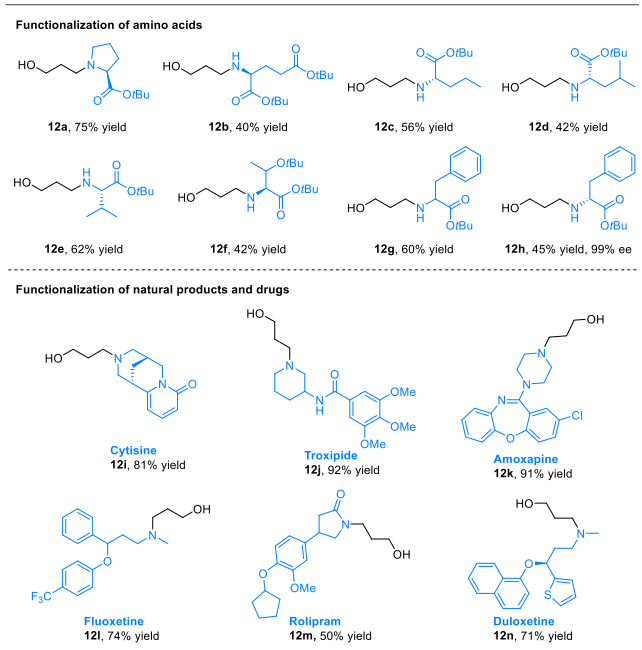



Figure 6. Functionalization of amino acids, natural products, and drugs. See SI for detailed reaction conditions.

**Gram-scale reaction and further synthetic applications.** The utility of the iron catalysis is still further seen in a gram-scale reaction and its synthetic application. The reaction of **7r** with **5a** at 10 mmol scale afforded 1.78 g of the hydroamination product **8r** (75% yield, Figure 7a). **8r** could serve as an intermediate, via **13**, for the synthesis of Urapidil,[26] a sympatholytic antihypertensive drug (Figure 7a). The hydroamidation products shown in Figure 4 could be transformed into

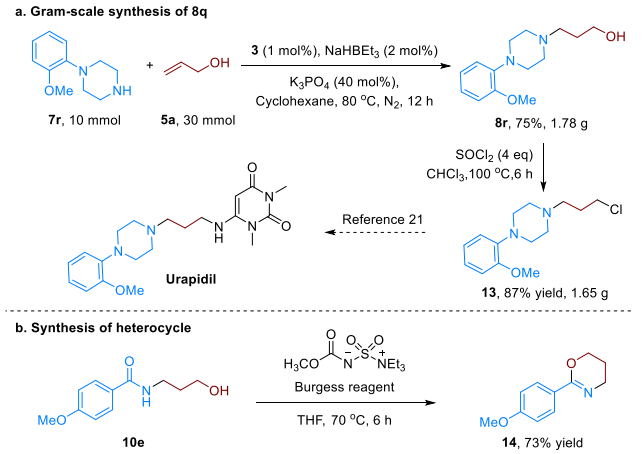



Figure 7. Gram scale reaction and an example of further synthetic applications. See SI for detailed reaction conditions.

heterocycles of potentially interesting bioactivities, as showcased by the dehydrative cyclization of **10e** to afford an dihydro-1,3-oxazine product **14** in 73% isolated yield (Figure 7b).[24b,27]

**Mechanistic considerations.** The hydroamination and hydroamidation reactions described may proceed via the pathway shown in Figure 1c. To gain evidence for the proposal, a series of experiments were performed. First, hydrogen gas was detected when allyl alcohol **5a** alone was subjected to the standard hydroamination conditions (See section 4.1 in the SI for details), and in the presence of $D_2$ under the same conditions, H/D exchange was observed at the α position of allyl alcohol (Figure 8a, see section 4.2 in the SI for details). These observations indicate that the iron catalyst is capable of reversible dehydrogenation/hydrogenation of the allylic alcohol. Second, on replacing **5a** with allyl acetate, no hydroamination was observed (Figure 8b, see section 4.3 in the SI for details), which supports an *α,β*-unsaturated aldehyde as intermediate. Third, HRMS experiments showed that acrolein, the product of **5a** dehydrogenation, could react with amine **7v** to afford a Michael addition product **15** as well as an iminium intermediate **16** under the standard conditions (Figure 8c). However, when the reaction was carried out in the presence of $H_2$ gas, **8v** was observed instead, suggesting that **15** was fully reduced to **8v** by the $H_2$. Interestingly, the cation **16** remained, indicating that **3** is more effective in catalyzing the reduction of a carbonyl group (Figure 8d). Finally, HRMS analysis of the crude reaction mixture of **7v** with **5a** revealed the presence of **16** and the hydroamination product **8v**, but no **15** (Figure 8e, see section 4.4 in SI for details). These results suggest that acrolein is an intermediate of the hydroamination/hydroamidation reaction, which is converted into an iminium cation upon reaction

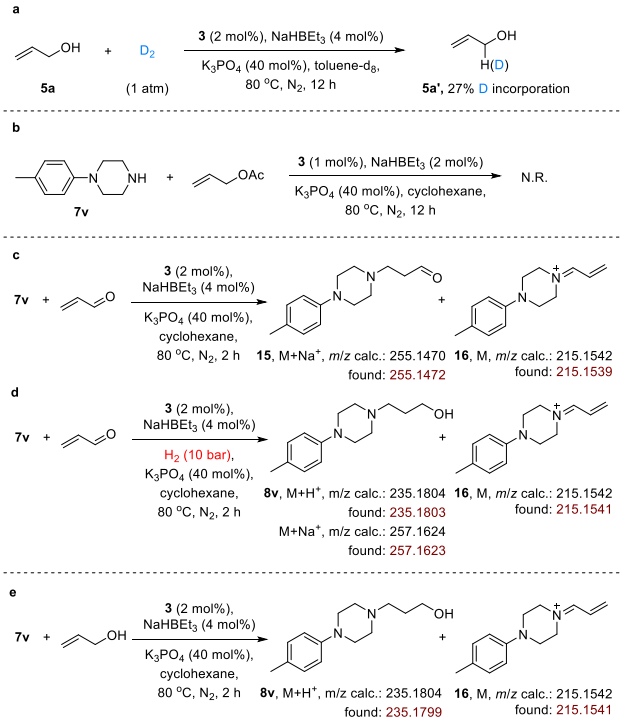



Figure 8. Reactions aimed to probe the mechanism.

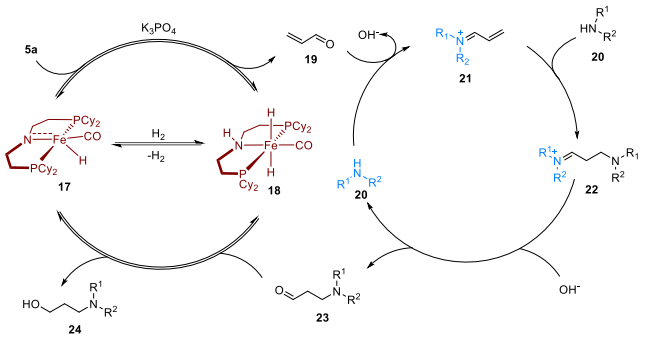


Figure 9. Proposed mechanism for the hydroamination/hydroamidation.

with a secondary amine and is thereby activated toward the subsequent aza-Michael addition.

Based on these experiments and the literature,[6,18] a more detailed mechanism is proposed and shown in Figure 9. In the presence of $NaBHEt_3$, the Fe complex **3** is activated to give the active catalyst **17**,[14f] which reversely dehydrogenates the allyl alcohol **5a** to give acrolein **19** and an iron-dihydride intermediate **18** in the presence of the base $K_3PO_4$ (See section 4.5 in the SI for the role of base). Acrolein then condenses with the amine **20** to form an activated Michael acceptor intermediate **21**, which undergoes aza-Michael addition with another amine **20** to give an intermediate **22**. Hydrolysis of the imine **22** affords an intermediate **23**, which is then reduced by **18**, affording the hydroamination product **24** while regenerating the catalytic species **17**. The formation of hydrogen gas indicates that the dihydride species **18** can undergo reversible dehydrogenation. Under catalytic turnover, the iminium intermediate **21** is observed, indicating the step of aza-Michael addition to be turnover limiting. The low activity of primary amines is in line with this assertion, as their condensation product with **5a**, a neutral imine, will be much less electrophilic than **21**.

## Conclusions

An iron-catalyzed hydroamination, as well as hydroamidation, of allylic alcohols has been developed. The catalytic system features exclusive anti-Markovnikov selectivity, mild reaction conditions, broad substrate scope, and good functional group tolerance. The protocol allows for the retention of stereochemistry of chiral substrates and functionalization of amino acids, natural products and drug molecules. Homoallylic alcohol is also shown to be viable. Mechanistic studies suggest that the reaction proceeds via two cooperating catalytic cycles, with the Fe-PNP complex catalyzing a dehydrogenation/hydrogenation process, while the amine substrate acting as an organocatalyst facilitating the Michael addition.

## ASSOCIATED CONTENT

**Supporting Information**.

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, spectroscopic traces for mechanistic studies and characterization data for products.

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### Notes

The authors declare no competing financial interests.

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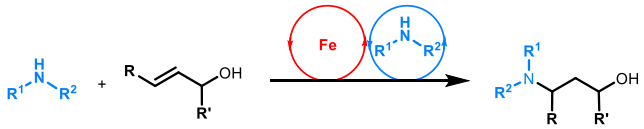


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- ☐ 76 examples
- ☐ Cheap and abundant catalyst
- ☐ Functionlization of complex molecules